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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,890	BRUSTLE, OLIVER	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,6,8-13,15,46-48,50 and 76-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6,8-13,15,46-48,50 and 76-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 23, 2004 (hereinafter referred to as "the response") has been entered. Claims 2, 6, 13, 15, and 47 have been amended. Claims 4, 5, 7, 14, 49, and 51 have been cancelled. Claims 76-99 have been newly added.

Accordingly, Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 23, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a non-tumorigenic cell composition derived from embryonic stem cells, the composition comprising about 100% isolated neural precursor cells having the ability to differentiate into neuronal cells, glial cells, or combinations thereof.

The specification defines a **neural precursor cell** as an "[i]mmature cell of the nervous system which has the potential to develop into mature nervous system cells such as neurons and glia (astrocytes and oligodendrocytes)" (page 7, lines 15-17).

The specification fails to provide an enabling disclosure for the claimed cell composition comprising "about 100% isolated neural precursor cells" because the specification only teaches how to produce cell compositions comprising around 66% neural precursor cells derived from ES cells. The instant specification discloses at page 24, lines 31-34 that immunofluorescent analysis of neural spheres demonstrated that 66% of the cells were nestin-positive neural precursor cells. Although the instant specification states that the methodology described permits the production of neural precursor cell compositions with a purity far exceeding 85% and further that the methodology permits the generation of neural precursor cells in a purity up to 100% (page 18, lines 25-32), there is no demonstration of cell compositions exceeding 66% neural precursor cells. The prior art discloses a methodology for obtaining compositions comprising 95% neural precursor cells (Okabe et al., 1996). These cell compositions were produced from ES cells by *in vitro* culture methods. Neither the prior art nor the instant specification teaches how to obtain a composition comprising 100% neural precursor cells.

At page 16, paragraph 6 of the response, Applicant argues that the 66% value referred to in the specification at page 24, refers to the fraction of nestin-positive cells detectable 5 days after plating ES cell-derived spheres in the absence of growth factors and that, once the ES cell-derived spheres are induced to differentiate, the cell composition comprises approximately 34% neurons, 30% astrocytes, and 6% oligodendrocytes. Applicants conclude that the composition comprises 100% neural precursors.

However, neurons, astrocytes, and oligodendrocytes are not neural precursor cells, but rather are differentiated cell types.

At page 17 of the response, Applicant asserts that the Declaration of Dr. Bruestle provides data indicating that the undifferentiated, tumorigenic ES cells have been essentially eliminated from the cell compositions of the present invention, and that neural precursor cells have been generated in unprecedented purity approaching 100%. Applicant further asserts that antibodies that bind to markers of both immature (nestin and A2B5) and differentiated (βIII-tubulin, GFAP, and O4) cells were used to determine the overall purity of the generated neural cells. Applicants state that "[t]he data demonstrates that the cell compositions of the present invention contain more than 99% **neural cells**" (emphasis added). This is quite a different statement from what is being claimed, which is a composition comprising about 100% neural **precursor** cells, not neural cells. Again, differentiated cells do not qualify as neural **precursor** cells, even according to the Applicant's own definition as noted above.

ES Cell Technology

The specification fails to provide an enabling disclosure for the preparation of embryonic stem (ES) cell-derived neural precursor cells from animals other than mice and humans because the guidance offered in the specification is limited to the use of mouse ES cells in the preparation of mouse neural precursor cells and specific guidance is not provided with regard to how one would have prepared ES cells from other species. Since ES cells are the starting material for generating the claimed compositions comprising neural precursor cells ES cell technology must be available to prepare the claimed compositions. The only species in which such technology was known was the mouse and, in November 1998, human ES cells became available in the art. At the time of filing the instant application, the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut (1997) acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which

contribute to the germ line in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. 1558, column 2, paragraph 1). Since ES cell technology was required to produce the claimed compositions, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed ES cell-derived neural precursor cell compositions for species other than mice and humans.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES cells and that "[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells" (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells. In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. The instant specification does not provide specific teachings with regard to the genetic modification of human ES cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the filing date of this application which is August 28, 2000, with priority claims to 12/18/98 and 12/19/97.

In view of the limited guidance provided in the specification for obtaining cell compositions with the requisite percentage of neural precursor cells as recited in the claims, the lack of applicable working

examples, the quantity of experimentation necessary to obtain the claimed cell compositions, and the unpredictability for producing cell compositions of a purity as high as 100%, undue experimentation would have been required for one skilled in the art to make and use the claimed cell compositions.

Pharmaceutical Compositions

Claims 46, 86, 97, and 99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to pharmaceutical compositions.

In addition to the enablement issues detailed above, the claims directed to pharmaceutical compositions are subject to the further enablement issues discussed below.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The following factors have been considered.

Nature of the invention and scope of the claims. The claims are drawn to pharmaceutical compositions comprising neural precursor cells. The claims are broad in scope, covering a variety of different types of neural precursor cells, including committed precursors, multipotent precursors, and neural stem cells. The compositions are non-tumorigenic. The cells may or may not be genetically modified. By using the term "pharmaceutical," the claims recite a specific intended use. Thus, the claims

are directed to compositions intended for therapeutic use. The only use contemplated in the specification for pharmaceutical compositions comprising neural precursor cells is for therapeutic transplantation. In order for the "how to use" component of the enablement requirement to be satisfied, at least one therapeutic use must be enabled for the claimed compositions. See MPEP 2164.01(c). When a compound or composition is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F. 2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

Amount of direction or guidance presented and the presence or absence of working examples. The examples of the specification are limited to producing neural precursor cells from mouse embryonic stem cells and xenotransplantation of these cells into embryonic rats or immunosuppressed adult rats with induced lesions of the striatum. Examples 4 and 5 describe xenotransplantation experiments where mouse ES cell-derived neural cell compositions are injected into either rat embryonic brain (myelin-deficient rats) or adult rat brain with ibotenic acid-induced striatal lesions. The experiments did not describe a therapeutic effect that would correlate to treatment of a human disease. The specification does not teach how to use the claimed cell compositions to achieve a therapeutic effect upon transplantation. The specification suggests that the pharmaceutical compositions can be used to treat a wide variety of neurological diseases of the CNS, including Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), Huntingtons disease, traumatic lesions of the brain and spinal cord, ischemic and hemorrhagic infarctions, hereditary atrophic disorders of the cerebellum and brain stem, motoneuron diseases, spinal muscular atrophies, adrenoleukodystrophy, and Pelizeaus-Merzbacher disease, as well as neoplastic disorders of the nervous system (page 9, line 32 to page 10 line 2). With regard to treatment of a neurological disease, the specification provides only general guidance rather than specific guidance. The specification does not offer specific guidance as to how the cells can be used therapeutically for any given disorder. No working examples demonstrate a therapeutic effect upon implantation of the claimed composition. The specification fails to provide any guidance relating to the

number of cells to inject, the site of injection, the extent of cellular persistence required and attainable in practice, and the duration of expression of any product needed, to provide any therapeutic benefit for the treatment of any disorder. Methods of treating CNS disorders by cell therapy or *ex vivo* gene therapy are in their infancy. Therefore, considerable guidance is needed.

State of the prior art and predictability of the art. The specification fails to provide an enabling disclosure for the therapeutic use of the claimed cell compositions. The specification fails to teach how to use the cells for a pharmaceutical use, i.e. for therapy. At the time the invention was made, successful implementation of cell therapy and gene therapy protocols was not routinely achievable by those skilled in the art.

While the specification suggests using the claimed compositions for treatment of a wide variety of CNS disorders and further suggests that certain genetic modifications could be made to produce cells that have a desired phenotype, no specific guidance is offered with regard to genetic modifications that could be used to produce a therapeutic effect. Thus, the following examples address the issue of cell therapy in general, but also apply to *ex vivo* gene therapy. Even under the best conditions, cell therapy in the central nervous system is highly unpredictable. For example, Milward et al. (1997) demonstrates that transplantation of neural stem cells to the CNS does not produce a therapeutic effect in a diseased animal. Milward et al. describes the transplantation of canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this resulted in the production of myelin by graft-derived cells. The authors report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. Yet despite all this, the clinical deficit of these animals was not ameliorated. Thus, it is clear that the production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome. Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells in vitro prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses the barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS and PNS axons. The specification does not offer any guidance as to how such obstacles could be overcome.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

In view of the quantity of experimentation necessary to determine appropriate parameters for using the claimed compositions to achieve a therapeutic outcome, and given the lack of applicable working examples directed to therapeutic transplantation, the limited guidance in the specification with regard to transplantation protocols and their applicability to pathologic conditions, the broad scope of the claims with regard to the wide variety of precursor cell types that could be used, the broad scope of the claims with regard to the wide variety of diseases covered and the type of protocol to be used, and further given the unpredictability in the art of therapeutic transplantation, undue experimentation would have

been required for one skilled in the art to use the claimed pharmaceutical compositions in therapeutic transplantation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are indefinite in their recitation of "or combinations thereof" because a cell cannot differentiate into a combination of two different cell types (i.e., a combination of neuronal cells and glial cells).

Claims 2, 3, 6, 8-13, 15, 46-48, 50, and 76-99 are indefinite in their recitation of "the neural precursor cells having the ability to differentiate into neuronal cells, glial cells, or combinations thereof" because it is unclear if the precursor cells have the ability to differentiate into all 3 cell types, including neurons, astrocytes, and oligodendrocytes, or if the precursors only have the ability to differentiated into **either** neuronal cells **or** glial cells. In other words, are the precursors multipotent or committed precursors?

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (571) 272-0548.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER